WEST Search History

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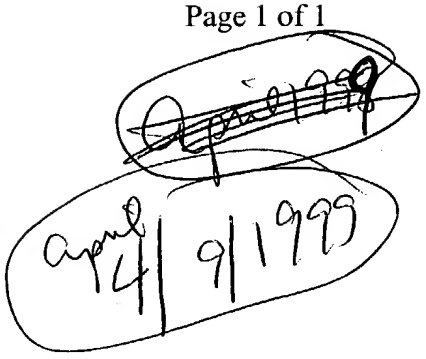

DATE: Thursday, February 12, 2004

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	DB=USPT; PLUR=YES; OP=AND		
☐	L1	insolub$ and (4954298 or 4917893).pn.	2
☐	L2	$polymer same hydrophilic same (protein$ or peptide or polypeptide or poly-peptide)	2876
☐	L3	L2 same micelle	22
☐	L4	l3 and surfact$	16
☐	L5	L4 and organic$	12
☐	L6	L5 and (aqueous or water or h20)	12
☐	L7	L6 and critical$	10
☐	L8	L7 and stabiliz$	4
☐	L9	l8 and l2	4
☐	L10	hydrophilic near5 surfact$	6205
☐	L11	L10 same l2	32
☐	L12	L11 and (mcm or micell$)	10
☐	L13	critical near3 micell$	1975
☐	L14	L13 same hydrophil$	335
☐	L15	L14 same l2	3

END OF SEARCH HISTORY

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Search Results - Record(s) 1 through 2 of 2 returned.

☐ 1. 4954298. 23 Sep 88; 04 Sep 90. Method for producing microcapsule. Yamamoto; Masaki, et al. 264/4.6; 264/4.1 424/461 424/462 424/493 424/497 514/800 514/885 514/963 604/891.1. A61K009/50 A61K009/52 A61K009/66 B01J013/02.

☐ 2. 4917893. 30 Sep 87; 17 Apr 90. Prolonged release microcapsules. Okada; Hiroaki, et al. 424/423; 424/433 424/497 424/499 424/500 428/402.2 514/2 514/800 514/843 514/963. A61K009/52 B01J013/02 A61F002/00.

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insolub$ and (4954298 or 4917893).pn.	2

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Search Results - Record(s) 1 through 12 of 12 returned.

☐ 1. 6521736. 14 Sep 01; 18 Feb 03. Amphiphilic polymeric materials. Watterson; Arthur C., et al. 528/272; 424/423 424/448 424/449 424/499 424/501. C08G063/02.

☐ 2. 6387406. 17 Jul 01; 14 May 02. Copolymer compositions for oral delivery. Kabanov; Alexander V., et al. 424/486; 424/422 514/772.1 514/772.3. A61K038/17.

☐ 3. 6359054. 08 Jan 99; 19 Mar 02. Polynucleotide compositions for intramuscular administration. Lemieux; Pierre M., et al. 524/505; 424/426 524/612 525/92A 525/92L 536/23.7 536/24.1 536/24.31 536/24.5. C08L053/00 C07H021/00.

☐ 4. 6322810. 18 May 00; 27 Nov 01. Materials and methods for making improved micelle compositions. Alkan-Onyuksel; Hayat, et al. 424/450; 424/1.21 424/812 424/9.321 424/9.51 424/94.3 428/402.2 436/829 514/21 514/937. A61K009/127.

☐ 5. 6322805. 12 Apr 00; 27 Nov 01. Biodegradable polymeric micelle-type drug composition and method for the preparation thereof. Kim; Sung-Chul, et al. 424/426; 424/486. A61F002/00 A61K009/14.

☐ 6. 6277410. 06 Feb 98; 21 Aug 01. Copolymer compositions for oral delivery. Kabanov; Alexander V., et al. 424/486; 424/422 514/772.1 514/772.3. A61K038/17.

☐ 7. 6218438. 17 Nov 99; 17 Apr 01. Copolymer compositions for treating viral infections. Alakhov; Valery, et al. 514/772.4; 514/502. A61K047/32 A61K031/295.

☐ 8. 6217886. 27 Jan 99; 17 Apr 01. Materials and methods for making improved micelle compositions. Onyuksel; Hayat, et al. 424/401; 264/4.1 264/4.3 264/4.6 424/1.21 424/450 424/9.321 424/9.51 514/2 514/21 514/937. A61K009/10 A61K009/127.

☐ 9. 6093391. 27 Feb 98; 25 Jul 00. Peptide copolymer compositions. Kabanov; Alexander V., et al. 424/85.1; 424/182.1 424/78.18 424/94.3 514/3 514/723. A61K045/08 A61K031/74 A61K038/28.

☐ 10. 5919434. 14 Mar 97; 06 Jul 99. Polymeric surfactant-encapsulated microbubbles and their use in ultrasound imaging. Dugstad; Harald, et al. 424/9.52; 424/489 424/501 427/213.3 427/213.36 428/402.21. A61K049/04 A61K009/16 B01J013/02 B32B005/16.

☐ 11. 5272094. 04 Mar 93; 21 Dec 93. Isolation of components from biological specimens via matrix solid phase dispersion. Barker; Steven A., et al. 436/518; 435/274 436/174 436/524 436/527 436/528. G01N033/543.

☐ 12. 3632342. 03 Mar 69; 04 Jan 72. PHOTOGRAPHIC ELEMENT CONTAINING ACRYLIC LATEX POLYMERS. Salesin; Eugene Dennis, et al. 430/496; 430/531 430/536 430/627 430/950. G03c001/76 G03c001/72.

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L6: Entry 1 of 12 File: USPT Feb 18, 2003

US-PAT-NO: 6521736
DOCUMENT-IDENTIFIER: US 6521736 B2

TITLE: Amphiphilic polymeric materials

DATE-ISSUED: February 18, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Watterson; Arthur C.	Nashua	NH		
Danprasert; Kunya	Bangkapi			TH
Diwan; Anil	West Haven	CT		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
University of Massachusetts	Boston	MA			02

APPL-NO: 09/ 952883 [PALM]
DATE FILED: September 14, 2001

PARENT-CASE:
CROSS-REFERENCE TO RELATED APPLICATION This invention claims the benefit of U.S. Provisional Application No. 60/232,937, filed Sep. 15, 2000, incorporated by reference in its entirety.

INT-CL: [07] C08 G 63/02

US-CL-ISSUED: 528/272; 424/423, 424/448, 424/449, 424/499, 424/501
US-CL-CURRENT: 528/272; 424/423, 424/448, 424/449, 424/499, 424/501

FIELD-OF-SEARCH: 528/271, 528/272, 424/501, 424/423, 424/499, 424/449, 424/448

PRIOR-ART-DISCLOSED:

OTHER PUBLICATIONS

Bundgaard (1986) "Design of Bioreversible Drug Derivatives and the Utility of the Double Prodrug Concept", Bioreversible Carriers in Drug Design Theory and Application Ch. 2, pp. 13-94.
Friis (1999) "Controlled-Release Oral Delivery Systems") in Polymer Preprints, American Cancer Society 40(1):252-369.
Erdmann et al. (1998) "Polymeric Prodrugs: Novel Polymers with Bioactive Components" Components" in Tailored Polymeric Materials for Controlled Delivery Systems Ch 5 pp. pp. 83-91.
Nagasaki et al. (1998) "The Reactive Polymeric Micelle, Convenient Tool for Targeting Drug Delivery System" in Tailored Polymeric Materials for Controlled Delivery Systems, American Chemical Society Ch 7 pp. 105-116.
Schwarte et al. (1998) "Cationic Hydrogels for Controlled Release of Proteins and Other Macromolecules" in Tailored Polymeric Materials for Controlled Delivery

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Search Results - Record(s) 1 through 2 of 2 returned.

☐ 1. Document ID: US 4954298 A

L1: Entry 1 of 2 File: USPT Sep 4, 1990

DOCUMENT-IDENTIFIER: US 4954298 A
TITLE: Method for producing microcapsule

Parent Case Text (29):
The polymer to be contained in the oil phase in carrying out the method according to this invention is a polymer which is scarcely soluble or insoluble in water and is biocompatible. Examples are such biodegradable polymers as aliphatic polymers (e.g. polylactic acid, polyglycolic acid, polycitric acid, polymalic acid), poly-.alpha.-cyanoacrylic acid esters, poly-.beta.-hydroxybutyric acid, polyalkylene oxalate (e.g. polytrimethylene oxalate, polytetramethylene oxalate), polyorthoesters, polyorthocarbonates and other polycarbonates (e.g. polyethylene carbonate, polyethylene-propylene carbonate), and polyamino acids (e.g. poly-.gamma.-benzyl-L-glutamic acid, poly-L-alanine, poly-.gamma.-methyl-L-glutamic acid). Other biocompatible high polymers are polystyrene, polyacrylic acid, polymethacrylic acid, acrylic acid-methacrylic acid copolymers, polyamides (nylon), polyethylene terephthalate (tetron), polyamino acids, silicone polymers, dextran stearate, ethylcellulose, acetyl-cellulose, nitrocellulose, polyurethanes, maleic anhydride-based copolymers, ethylene-vinyl acetate copolymers, polyvinyl acetate, polyvinyl alcohol, polyacrylamide, etc. These polymers may be homopolymers or copolymers of two or more monomers, or mixtures of the polymers. They may also be in the salt form.

Full | Title | Citation | Front | Review | Classification | Date | Reference | [illegible] | Claims | KWIC | Draw De

☐ 2. Document ID: US 4917893 A

L1: Entry 2 of 2 File: USPT Apr 17, 1990

DOCUMENT-IDENTIFIER: US 4917893 A
TITLE: Prolonged release microcapsules

Brief Summary Text (26):
The aforementioned polymer substance employed in the oil layer are polymers hardly soluble or insoluble in water and biocompatible. As examples of such polymer substance may be mentioned biodegradable aliphatic polymers (e.g. polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, etc.), poly-.alpha.-

cyanoacrylic acid esters, poly-.beta.-hydroxybutyric acid, polyalkylene oxalate (e.g. polytrimethylene oxalate, polytetramethylene oxalate, etc.), poly(ortho-esters), poly(ortho-carbonate), other polycarbonate (e.g. polyethylene carbonate, polyethylene propylene carbonate, etc.), polyamino acids (e.g. poly-.gamma.-benzyl-L-glutamic acid, poly-L-alanine, poly-.gamma.-methyl-L-glutamic acid, etc.) and so on. As further examples of biocompatible polymer substance may be mentioned, polystyrene, polyacrylic acid, polymethacrylic acid, copolymer of acrylic acid and methacrylic acid, nylon, tetron, polyamino acid, silicone polymer, dextran stearate, stearate, ethylcellulose, acetylcellulose, nitrocellulose, polyurethane, maleic anhydride copolymers, ethylene-vinyl acetate copolymer, polyvinyl acetate, polyvinyl polyvinyl alcohol, polyacrylamide, etc. These polymer substances may be used alone or in the form of copolymers or mixtures of two or more species or of salts.

Terms	Documents
insolub$ and (4954298 or 4917893).pn.	2

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L1: Entry 1 of 2 File: USPT Sep 4, 1990

US-PAT-NO: 4954298
DOCUMENT-IDENTIFIER: US 4954298 A

TITLE: Method for producing microcapsule

DATE-ISSUED: September 4, 1990

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Yamamoto; Masaki	Osaka			JP
Takada; Shigeyuki	Suita			JP
Ogawa; Yasuaki	Ibaraki, all			JP

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Takeda Chemical Industries, Ltd.	Osaka			JP	03

DISCLAIMER DATE: 20040324

APPL-NO: 07/ 249198 [PALM]
DATE FILED: September 23, 1988

PARENT-CASE:
This application is a continuation of U.S. application Ser. No. 826,968, filed Feb. 7, 1986, now abandoned. This invention relates to a method for producing sustained-release microcapsules containing a water-soluble drug. For drugs required to be administered for a prolonged period, various dosage forms have been proposed. Among them, there is disclosed in European Patent Application Publication No. 52,510A a method of microencapsulation by phase separation using a coacervation agent such as a mineral oil or a vegetable oil. Microcapsules obtained by the above-mentioned method have a drawback in that the particles are apt to adhere to one another in their production process. Under these circumstances, the intensive studies were carried out in order to develop sustained release drug preparations. As a result, it was found that microcapsules having favorable properties can be obtained efficiently with a high rate of drug take-up into the microcapsules when, in the process of forming a three-phase emulsion for microencapsulation by an in water drying, the viscosity of the W/O emulsion for preparing the three-phase W/O/W emulsion is adjusted to about 150 to about 10,000 cp. Further research work based on this finding has now led to completion of the present invention. Thus this invention is directed to: a method of preparing sustained-release microcapsules containing a water-soluble drug , which comprises preparing a W/O emulsion composed of a water-soluble drug-containing solution as the inner aqueous phase and a polymer-containing solution as the oil phase adjusting the viscosity of the W/O emulsion used in preparing the W/O/W emulsion to from about 150 to about 10,000 cp , dispersing said emulsion in an aqueous phase and subjecting the resulting W/O/W emulsion to an in-water drying. The viscosity value mentioned herein is measured with an Ubbelohde viscometer in accordance with the Japanese Pharmacopeia. This is dynamic viscosity value, and "cp" stands for centipoise. The water-soluble drug to be used in the practice of this invention is highly hydrophilic and has a

small oil/water distribution coefficient which, when given in terms of octanol/water octanol/water distribution coefficient, for instance, is not greater than about 0.1. 0.1. Said water-soluble drug includes, but is not particularly limited to, physiologically active polypeptides, other antibiotics, antitumor agents, antipyretics, analgesics, antiinflammatory agents, antitussives and expectorants, sedatives, muscle relaxants, antiepileptics, antiulcer agents, antidepressants, antiallergic agents, cardiotonics, antiarrhythmic agents, vasodilators, antihypotensive diuretics, antidiabetic agents, anticoagulants, hemostatic agents, antitubercular agents, hormones and narcotic antagonists. The physiologically active active polypeptides usable in the practice of this invention contain two or more amino acids and preferably have a molecular weight of about 200 to about 80,000. Examples of said polypeptides include luteinizing hormone releasing hormone (LH-RH), RH), derivatives thereof having LH-RH like activity, i.e. the polypeptides of the formula: (Pyr)Glu-R.sub.1 -Trp-Ser-R.sub.2 -R.sub.3 -R.sub.4 -Arg-Pro-R.sub.5 (I) wherein R.sub.1 is His, Tyr, Trp or p-NH.sub.2 -Phe, R.sub.2 is Tyr or Phe, R.sub.3 is Gly or a D-amino acid residue, R.sub.4 is Leu, Ile or Nle and R.sub.5 is Gly-NH-R.sub.6 (R.sub.6 is H or a lower alkyl group which may optionally be substituted by hydroxy) or NH-R.sub.6 (R.sub.6 is as defined above), and salts thereof [see U.S. Pat. Nos. 3,853,837, 4,008,209 and 3,972,859, British Patent No. 1,423,083, and Proceedings of the National Academy of Sciences of the United States of America, volume 78, pages 6509-6512 (1981)]. Referring to the above formula (I), the D-amino acid residue represented by R.sub.3 is, for example, an .alpha.-D-amino acid residue residue containing up to 9 carbon atoms (e.g. D-Leu, Ile, Nle, Val, NVal, Abu, Phe, Phg, Ser, Tyr, Met, Ala, Trp, .alpha.-Aibu). It may have an appropriate protective group (e.g. t-butyl, t-butoxy, t-butoxycarbonyl, naphtyl). An acid addition salt or metal complex of the peptide (I) can of course be used in the same manner as the peptide (I). In abbreviating the amino acids, peptides, protective groups and so on as used in specifying the polypeptides of formula (I), there are used the abbreviations according to the IUPAC-IUB Commission on Biological Nomenclature or the abbreviations commonly used in the relevant field of art. For those amino acids which involve optical isomerism, each abbreviation, unless otherwise indicated, refers to the L-form. In this specification, the acetate of the polypeptide of the above formula (I) wherein R.sub.1 =His, R.sub.2 =Tyr, R.sub.3 =D-Leu, R.sub.4 =Leu and R.sub.5 = NHCH.sub.2 -CH.sub.3 is called "TAP-144". Said polypeptide in acetate form has the generic name "leuprolide". Said polypeptides further include LH-RH antagonists (see U.S. Pat. Nos. 4,086,219, 4,124,577, 4,253,997, 4,317,815, 329,526 and 368,702). Said polypeptides also include, for example, insulin, somatostatin, somatostatin derivatives (see U.S. Pat. Nos. 4,087,390, 4,093,574, 4,100,117 and 4,253,998), growth hormones, prolactin, adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (MSH), thyrotropin-releasing hormone (TRH), salts and and derivatives thereof (see U.S. Pat. Nos. 3,957,247 and 4,100,152), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), vasopressin, vasopressin derivatives [desmopressin [see Folia Endocrinologica Endocrinologica Japonica, volume 54, No. 5, pages 676-691 (1978)]], oxytocin, calcitonin, parathyroid hormone, glucagon, gastrin, secretin, pancreozymin, cholecystokinin, angiotensin, human placental lactogen, human chorionic gonadotropin gonadotropin (HCG), enkephalin, enkephalin derivatives (see U.S. Pat. No. 4,277,394 and European Patent Application Publication No. 31567A), endorphin, kyotorphin, interferons (.alpha., .beta. and .gamma.), interleukins (I, II and III), taftsin, thymopoietin, thymosin, thymostimulin, thymic humoral factor (THF), serum thymic factor (STF or FTS) and derivatives thereof (see U.S. Pat. No. 4,229,438), and other other thymic factors [Igaku no Ayumi (Medicine in Progress), volume 125, No. 10, pages 835-843 (1983)], tumor necrosis factor (TNF), colony stimulating factor (CSF), (CSF), motilin, dinorphin, bombesin, neurotensin, cerulein, bradykinin, urokinase, asparaginase, kallikrein, substance P, nerve growth factor, blood coagulation factors VIII and IX, lysozyme chloride, polymixin B, colistin, gramicidin, bacitracin, protein synthesis-stimulating peptides (British Patent No. 8,232,082), gastric inhibitory polypeptide (GIP), vasoactive intestinal polypeptide (VIP), platelet-derived growth factor (PDGF), growth hormone-releasing factor (GRF, somatocrinin), bone morphagenetic protein (BMP) and epidermal growth factor (EGF).

The antitumor agents mentioned above include, among others, bleomycin hydrochloride, hydrochloride, methotrexate, actinomycin D, mitomycin C, vinblastine sulfate, vincristine sulfate, daunorubicin hydrochloride, adriamycin, neocarcinostatin, cytosine arabinoside, fluorouracil, tetrahydrofuryl-5-fluorouracil, krestin, picibanil lentinan, levamisole, bestatin, azimexon, glycyrrhizin, poly I:C, poly A:U A:U and poly ICLC. The antibiotics mentioned above include, among others, gentamicin, dibekacin, kanendomycin, lividomycin, tobramycin, amikacin, fradiomycin, fradiomycin, sisomicin, tetracycline hydrochloride, oxytetracycline hydrochloride, rolitetracycline, doxycycine hydrochloride, ampicillin, piperacillin, ticarcillin, cephalotin, cephaloridine, cefotiam, cefsulodine, cefmenoxime, cefmetazole, cefazolin, cefotaxime, cefoperazone, ceftizoxime, moxalactam, thienamycin, sulfazecin and azthreonam. The antipyretic, analgesic and antiinflammatory agents mentioned above include, among others, sodium salicylate, sulpyrine, sodium flufenamate, sodium diclofenac, sodium indomethacin, morphine hydrochloride, pethidine hydrochloride, levorphanol tartrate and oxymorphone. The antitussives and expectorants include ephedrine hydrochloride, methylephedrine hydrochloride, noscapine hydrochloride, codeine phosphate, dihydrocodeine phosphate, alloclamide hydrochloride, chlophedianol hydrochloride, picoperidamine hydrochloride, cloperastine, protokylol hydrochloride, isoproterenol hydrochloride, salbutamol sulfate and terbutaline sulfate, among others. The sedatives include chlorpromazine hydrochloride, prochlorperazine, trifluoperazine, atropine sulfate, scopolamine methyl bromide, and so forth. The muscle relaxants include, for example, pridinol methanesulfonate, tubocurarine chloride and pancuronium bromide. The antiepileptics include sodium phenytoin, ethosuximide, sodium acetazolamide chlordiazepoxide hydrochloride, etc. The antiulcer agents include, among others, metoclopramide and histidine hydrochloride. The antidepressants include imipramine, clomipramine, noxiptiline and phenelzine sulfate, amongst others. The antiallergic agents include, include, for instance, diphenhydramine hydrochloride, chlorpheniramine maleate, tripelenamine hydrochloride, methdilazine hydrochloride, clemizole hydrochloride, diphenylpyraline hydrochloride and methoxyphenamine hydrochloride. The cardiotonics include, among others, trans-.pi.-oxocamphor, theophillol, aminophylline and etilefrine hydrochloride. The antiarrhythmic agents include propranolol hydrochloride, alprenolol hydrochloride, bufetolol hydrochloride, oxyprenolol hydrochloride, etc. The vasodilators include oxyfedrine hydrochloride, diltiazem hydrochloride, tolazoline hydrochloride, hexobendine and bamethan sulfate, among others. The hypotensive diuretics include hexamethonium bromide, pentolinium, mecamylamine hydrochloride, ecarazine hydrochloride, clonidine hydrochloride, etc. The antidiuretic agents include, among others, sodium glymidine, glypizide, phenformin hydrochloride, buformin hydrochloride and metformin. The anticoagulants include sodium heparin and sodium citrate, among others. The hemostatic agents include thromboplastin, thrombin, menadione sodium bisulfite, acetomenaphthone, .epsilon.-aminocaproic acid, tranexamic acid, carbozochrome sodium sulfate, adrenochrome monoaminoguanidine methanesulfonate, and so forth. The antituberculous agents include, among others, isoniazide, ethanbutol and sodium p-aminosalicylate. The hormones include, among others, prednisolone succinate, prednisolone sodium phosphate, dexamethasone sodium sulfate, betamethasone sodium phosphate, hexestrol diphosphate, hexestrol diacetate and methimazole. The narcotic antagonists include levallorphan tartrate, nalorphine hydrochloride and neloxone hydrochloride, among others. The above-mentioned water-soluble drugs are used in amounts selected depending on the kind of drug, desired pharmacological effects and duration of the effects, among others, and the concentration in the inner aqueous phase is selected generally within the range about 0.001% to about 70% (weight/weight), preferably within the range of 0.01% to 50% (weight/weight). In carrying out the method according to this invention, the viscosity of the inner aqueous phase may be increased by further adding a drug retaining substance to the inner aqueous phase. The drug retaining substance mentioned above is a substance which is soluble in water but is hardly soluble in the organic solvent in the oil phase and, when dissolved in water, gives a highly viscous semisolid or, when placed in a water-dissolved state under the action of some external factor, for instance temperature, pH, metal ion (e.g. Cu.sup.++, Al.sup.+++, Zn.sup.++), organic acid (e.g. tartaric

acid, citric acid, tannic acid) or salt thereof (e.g. calcium citrate) or chemical condensing agent (e.g. glutaraldehyde, acetaldehyde), gives a semisolid or solid matrix as a result of marked increase of viscosity caused by said external factor. Examples of said drug retaining substance are natural or synthetic gums or high-molecular compounds. The natural gums include gum acacia, Irish moss, karaya gum, gum tragacanth, gum guaiac, xanthan gum and locust bean gum. The natural high molecular compounds include proteins, such as casein, gelatin, collagen, albumin (e.g. human serum albumin), globulin and fibrin, and carbohydrates, such as cellulose, dextrin, pectin, starch, agar and mannan. They may be used either as such such or in the form of synthetic gums resulting from partial chemical modification, for example esters or ethers derived from the above-mentioned natural gums (e.g. methylcellulose, ethylcellulose, carboxymethyl-cellulose, gelatin succinate), hydrolyzates thereof (e.g. sodium alginate, sodium pectinate), or salts of these. The synthetic high-molecular compounds include, among others, polyvinyl compounds (e.g. polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl methyl ether, polyvinyl ether), polycarboxylic acids [e.g. polyacrylic acid, polymethacrylic acid, Carbopol (Goodrich)], polyethylene compounds (e.g. polyethylene glycol), polysaccharides (e.g. polysucrose, polyglucose, polylactose), and salts of these. Also included within the scope of drug retaining substances are substances capable of giving high-high-molecular compounds as a result of condensation or cross-linking which proceeds proceeds under the action of the external factor mentioned above. Among these drug retaining substances, there are particularly preferable gelatin, albumin, pectin and and agar. The drug retaining substances may be used either alone or in combination. The polymer to be contained in the oil phase in carrying out the method according to to this invention is a polymer which is scarcely soluble or insoluble in water and is biocompatible. Examples are such biodegradable polymers as aliphatic polymers (e.g. polylactic acid, polyglycolic acid, polycitric acid, polymalic acid), poly-.alpha.-cyanoacrylic acid esters, poly-.beta.-hydroxybutyric acid, polyalkylene oxalate (e.g. polytrimethylene oxalate, polytetramethylene oxalate), polyorthoesters, polyorthocarbonates and other polycarbonates (e.g. polyethylene carbonate, polyethylene-propylene carbonate), and polyamino acids (e.g. poly-.gamma.-benzyl-L-glutamic acid, poly-L-alanine, poly-.gamma.-methyl-L-glutamic acid). Other biocompatible high polymers are polystyrene, polyacrylic acid, polymethacrylic acid, acrylic acid-methacrylic acid copolymers, polyamides (nylon), polyethylene terephthalate (tetron), polyamino acids, silicone polymers, dextran stearate, ethylcellulose, acetyl-cellulose, nitrocellulose, polyurethanes, maleic anhydride-based copolymers, ethylene-vinyl acetate copolymers, polyvinyl acetate, polyvinyl alcohol, polyacrylamide, etc. These polymers may be homopolymers or copolymers of two or more monomers, or mixtures of the polymers. They may also be in the salt form. Among these polymers, particularly preferred for use in injections are biodegradable polymers, most preferably polylactic acid, lactic acid-glycolic acid copolymer and mixtures thereof. The ratio of lactic acid to glycolic acid in the copolymer is preferably about 100/0 to 50/50 (weight %) preferably about 50 to 95 weight % of lactic acid and about 50 to 5 weight % of glycolic acid, more preferably about 60 to 95 weight % of lactic acid and about 40 to 5 weight % of glycolic acid, still more preferably about 60 to 85 weight % of lactic acid and about 40 to 15 weight % of glycolic acid. The ratio is especially preferably about 75.+-.2 mole % of lactic acid and about 25.+-.2 mole % of glycolic acid. The polymers for use in this invention preferably have an average molecular weight of about 1,000 to about 800,000, more preferably about 2,000 to about 100,000. The lactic acid-glycolic acid copolymers still more preferably have an average molecular weight of about 5000 to about 30000. These polymers are used in amounts to be selected depending on the intensity of pharmacological activity of the water-soluble drug, drug release rate, the duration and other factors. For instance, these are used as the microcapsule bases in an amount of about 3 to 10,000 parts by weight, preferably about 5 to about 100 parts by weight, per part by weight of the water-soluble drug. The solution (oil phase) containing the above polymer is that of the polymer in an organic solvent. Said organic solvent may be any organic solvent which has a boiling point not higher than about 120.degree. C. and hardly miscible with water. Examples are halogenated alkanes (e.g.

dichloromethane, chloroform, chloroethane, trichloroethane, carbon tetrachloride), ethyl acetate, ethyl ether, cyclohexane, benzene, and toluene. These may be used in admixture of two or more. In carrying out the microencapsulation method according to to this invention, water is added to the water-soluble drug to prepare the inner aqueous phase. Here, the above-mentioned drug retaining substance may further be added. To said inner aqueous phase, there may be added a pH-adjusting agent for maintaining the stability or solubility of the water-soluble drug, such as carbonic acid, acetic acid, oxalic acid, citric acid, tartaric acid, succinic acid, phosphoric acid, the sodium or potassium salt of the above compound, hydrochloric acid or sodium hydroxide. There may further be added a stabilizer for the water-soluble drug such as albumin, gelatin, citric acid, sodium ethylenediaminetetraacetate, dextrin or sodium hydrogen sulfite, or a preservative such as a para-hydroxybenzoic acid ester (e.g. methylparaben, propylparaben), benzyl benzyl alcohol, chlorobutanol or thimerosal. The thus-obtained aqueous solution for use as the inner aqueous phase is added to a polymer-containing solution (oil phase), followed by an emulsification procedure to give a W/O emulsion. For said emulsification procedure, a known method of effecting dispersion is used. Said method is, for example, the intermittent shaking method, the mixer method using a propeller-shaped stirrer, a turbine-shaped stirrer or the like, the colloid mill method, the homogenizer method or the ultrasonication method. The thus-prepared W/O emulsion is then emulsified into a W/O/W triplicate-phase emulsion and subjected to an in- water drying. Thus, said W/O emulsion is further added to a third aqueous phase to give a W/O/W emulsion and thereafter the solvent in the oil phase is removed to give microcapsules. To the external aqueous phase, there may be added an emulsifying agent. As the emulsifying agent, there may be used any one capable of forming generally a stable O/W emulsion, for example an anionic surfactant (e.g. sodium oleate, sodium stearate, sodium lauryl sulfate), a nonionic surfactant [e.g. polyoxyethylenesorbitan fatty acid ester (Tween 80, Tween 60, products of Atlas Powder Co., U.S.A.), a polyoxyethylene castor oil derivative (HCO-60, HCO-50, products of Nikko Chemicals, Japan)], polyvinyl pyrrolidone, polyvinyl alcohol, carboxymethylcellulose, lecithin or gelatin. Such emulsifiers may be used either alone or in combination of some of them. The emulsifying agent concentration may suitably be selected within the range of about 0.01% to 20%, preferably within the range of about 0.05% to 10%. The viscosity of the W/O emulsion for preparing the W/O/W emulsion is adjusted to about 150 cp to 10,000 cp, preferably about 150 cp to 5,000 cp. In adjusting the viscosity, there may be used the following means or a combination thereof, for instance: To increase the polymer concentration in the oil phase; To adjust the ratio in amount between the aqueous phase and the oil phase; To To adjust the temperature of said W/O emulsion; To adjust the temperature of the external aqueous phase; or To adjust the temperature of the W/O emulsion with a line line heater or cooler or the like in infusing the W/O emulsion into the external aqueous phase. What is important in taking such measures as mentioned above is only that the W/O emulsion has a viscosity of about 150 cp to 10,000 cp when it is made up into a W/O/W emulsion. In adjusting the viscosity of the W/O emulsion by taking one or more of the above procedures, the polymer concentration in the oil phase, when adjusted, is preferably adjusted to about 10 to 80% (weight by weight), although the preferable range of such concentration is not specified generally but may vary depending on the kind of polymer, kind of solvent and other factors. The adjusting the viscosity of the W/O emulsion in the above manner is preferably carried out so that the W/O ratio falls within the range of about 1% to 50% (volume by volume), although the preferable range of such ratio is not specified generally but may depend on the kind and amount of water-soluble drug and properties of the oil phase. In adjusting the viscosity of the W/O emulsion in the above manner, the temperature of the W/O emulsion is generally regulated to from about -20.degree. C. to the boiling point of the organic solvent used, preferably about 0.degree. C. to 30.degree. C. In cases where the polymer concentration in the oil phase has been adjusted or in cases where the ratio between the aqueous phase and the oil phase has has been adjusted, the viscosity of the W/O emulsion can be also adjusted on the occasion of preparing the W/O emulsion. In cases where the viscosity of the W/O emulsion is adjusted by regulating the temperature of the W/O emulsion, the

temperature of said W/O emulsion is adjusted, for example on the occasion of adding the W/O emulsion to the external aqueous phase. The viscosity adjustment may also be be effected by adjusting in advance the temperature of the external aqueous phase on on the occasion of adding the W/O emulsion to the external aqueous phase so that the the temperature of the W/O emulsion can be adjusted when the W/O/W emulsion is prepared. For removing the solvent from the oil phase in subjecting the W/O/W emulsion to an in-water drying, any of the common methods in general use is employed. Thus, the solvent is removed, for example by simply allowing the W/O/W emulsion to stand under stirring, by heating slowly said emulsion, by blowing nitrogen gas or the like onto said emulsion, by gradually reducing the pressure while stirring with a propeller-shaped stirrer or a magnetic stirrer, or by using a rotary evaporator while adjusting the degree of vacuum. In the step of solvent removal, the required time can be reduced by gradually warming the W/O/W emulsion after the progress of solidification of the polymer to a certain extent, to thereby rendering the solvent removal more complete. The thus-produced microcapsules are collected by centrifugation or filtration, rinsed several times with distilled water water to thereby remove the free water-soluble drug portion adhering to the microcapsule surface and other substances, and, if necessary, warmed under reduced pressure to thereby remove the moisture in microcapsules and the solvent in the microcapsule wall more completely. The microcapsules obtained in the above manner are sieved as necessary to eliminate excessively large microcapsules. For use in the the form of suspensions depending on the extent of the sustained-release property, the microcapsules may have a grain size within the range in which the dispersibility dispersibility and penetration requirements are met. Thus, for example, they may have an average grain size within the range of about 0.5 to 400 .mu.m, desirably and and preferably within the range of about 2 to 200 .mu.m, more preferably about 2 to 100 .mu.m. In this manner, the rate of take-up of the water-soluble drug, which is the active ingredient, into microcapsules can be increased by using the method according to this invention. Furthermore, the use of a smaller amount of organic solvent in the production process is sufficient as compared with the process involving drying in the oil phase. From the above and other viewpoints, the method according to this invention is advantageous in commercial microcapsule production. The microcapsules produced by the method according to this invention have many advantages. For instance, they scarcely undergo aggregation or cohesion to one another during the production step. There can be obtained microcapsules which are satisfactorily spherical in shape. The step of removing the solvent from the oil phase is easy to control, whereby the surface structure of microcapsules, which is decisive for the rate of drug release (inclusive, e.g. of the number and size of pores which are to serve as main routes of drug release), can be controlled. The microcapsules produced by the method according to this invention can be administered administered to the living body by implantation thereof as such. They may also be administered in various dosage forms and thus can be used as raw material in producing such dosage forms. The injection form is preferably as the dosage form mentioned above. For instance, in making up the microcapsules according to this invention for an injection, the microcapsules according to the invention are dispersed in an aqueous medium together with a dispersing agent (e.g. Tween 80, HCO-HCO-60, carboxymethylcellulose, sodium alginate), a preservative (e.g. methylparaben, propylparaben), an isotonizing agent (e.g. sodium chloride, mannitol, mannitol, sorbitol, glucose). Such suspension can serve as a sustained-release injection. Furthermore, the above microencapsulated sustained-release injection can be converted to a more stable, sustained-release injection by adding an additional excipient (e.g. mannitol, sorbitol, lactose, glucose), redispersing the resulting mixture and effecting solidification by freeze drying or spray drying with simultaneous addition of distilled water for injection or some appropriate dispersing agent. The dose of the sustained-release preparation according to this invention may vary depending on the kind and amount of the water-soluble drug, which which is the active ingredient, dosage form, duration of drug release, recipient animal (e.g. warm-blooded animals such as mouse, rat, horse, cattle, human) and purpose of administration but should be within the range of effective dose of said active ingredient. For example, the single dose per said animal of the microcapsules

microcapsules can adequately be selected within the range of about 0.01 to 200 mg/kg mg/kg body weight, preferable about 0.2 to 40 mg/kg, still more preferably about 0.2 0.2 to 20 mg/kg or 0.2 to 6 mg/kg. The volume of the suspension for administering as as the above-mentioned injection can adequately be selected within the range of about 0.1 to 10 ml, preferably about 0.1 to 5 ml, more preferably about 0.5 to 3 ml. ml. In this manner, there is obtained a pharmaceutical composition prepared in the form of microcapsules which comprises an effective but greater amount of the water-soluble drug as compared with the ordinary single dose and a biocompatible high polymer and is capable of releasing the drug continuously over a prolonged period of of time. The sustained-release preparation according to the present invention has the following advantages, among others: (1) Sustained-release of the water-soluble drug can be attained in various dosage forms. In particular, where a long-term treatment with an injection is required, the desired pharmacological effects can be achieved in a stable manner by injection of the preparation once a week, once a month, or even once a year, instead of daily administration. Thus, said preparation can achieve a sustained drug release over a longer period as compared with the prior prior art sustained-release preparations. (2) When the preparation in which a biodegradable polymer is used is administered in the form of an injection, such surgical operation as implantation is no more required but the preparation can be administered subcutaneously or intramuscularly with ease in quite the same manner as as the ordinary suspension injections. There is no need for taking it out again from from the body, because the biodegradable polymer is used. The preparation can also be administered directly to tumors, the site of inflammation or the site where there there is a receptor, for instance, whereby systemic side effects can be reduced and the drug can be allowed to act on a target organ efficiently for a long period of time. Potentiation of the drug activity is thus expected. Furthermore, the preparation can be administered intraarterially in the vasoembolic therapy for kidney cancer, lung cancer and so forth as proposed by Kato et al. [Lancet, volume II, pages 479-480 (1979)]. (3) The release of the active ingredient is continuous, so that, in case of , for instance, hormone antagonists or receptor antagonists stronger pharmacological effects are obtained as compared with daily or frequent administration. (4) As compared with the conventional method of production of microcapsules which comprises preparing a W/O/W triple-phase emulsion and subjecting subjecting the emulsion to an in-water drying method, the method according to this invention makes it possible to allow the water-soluble drug, which is the active ingredient, to be taken up into microcapsules efficiently. In addition, there can be be obtained fine microcapsules having a good degree of sphericity. In accordance with the method of this invention, the rate of water-soluble drug take-up into microcapsules can be increased markedly by adjusting the viscosity of the W/O emulsion to a value higher than that employed in the conventional processes. Accordingly, sustained-release microcapsules containing a water-soluble drug can be produced with advantage.

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U.S. PATENT DOCUMENTS

Search Selected | Search ALL | Clear

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	3043782	July 1962	Jensen	427/213.33 X
☐	3523906	August 1970	Vrancken et al.	264/4.6
☐	3539465	November 1970	Hiestand et al.	264/4.3 X
☐	4384975	May 1983	Fong	424/496 X
☐	4652441	March 1987	Okada et al.	264/4.6 X

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
1169090	June 1984	CA	514/4
0145240	June 1985	EP	264/4.6
2491351	April 1982	FR	
929402	June 1963	GB	
1405108	September 1975	GB	
2088314	June 1982	GB	

OTHER PUBLICATIONS

The Theory and Practice of Industrial Pharmacy, edited by L. Lachman et al., Lea & Febiger, Philadelphia, 1970, pp. 384-391.
European Search Report, European Patent Appln. No. 86300308.

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ABSTRACT:

Microcapsules are advantageously produced with high take-up of a water-soluble drug by preparing a W/O emulsion composed of a water-soluble drug-containing solution as the inner aqueous phase and a polymer-containing solution as the oil phase, dispersing said emulsion in an aqueous phase and subjecting the resulting W/O/W emulsion to an in-water drying, wherein the viscosity of the W/O emulsion used in preparing the W/O/W emulsion is adjusted to about 150 to about 10,000 centipoises.

20 Claims, 0 Drawing figures

Systems, American Chemical Society Ch 3 pp. 56-66.
Shalaby (1998) "Injectable Absorbable Gel-Formers for the Controlled Release of Bioactive Agents-Drugs" in Tailored Polymeric Materials for Controlled Delivery Systems, American Chemical Society Ch 9 pp. 125-128.
Slomkowski et al. (1998) "Direct Synthesis of Polyester Microsphers, Potential Carriers of Bioactive Compounds" in Tailored Polymeric Materials for Controlled Delivery Systems, Ch 11 pp. 143-153.
Abuchowski et al. "Alteration of Immunological Properties of Bovine Serum Albumin by by Covalent Attachment of Polyethylene Glycol", (1977) J. of Biol. Chem. 252 (11):3578-3581.
Aldrovandi et al. "The SCID-hu Mouse As Model for HIV-1 Infection", (1993) Nature 363:732-736.
Alexander et al. "Investigation of (Oxodioxolenyl)methyl Carbamates as Nonchiral Bioreversible Prodrug Moieties for Chiral Amines", (1996) J. Med. Chem. 39:480-486.

Alexander et al. "(Acyloxy) alkyl Carbamates as Novel Bioreversible Prodrugs for Amines: Increased Permeation through Biological Membranes", (1988) J. Med. Chem. 31:318-322.
Alpegiani et al. "On The Preparation of 4-Hydroxymethyl-5-Methyl-1,3-Dioxol-2-One", (1992) Synth. Commun. 22(9):1277-1282.
Amado et al. "Reconstitution of Human Thymic Implants Is Limited by Human Immunodeficiency Virus Breakthrough during Antiretroviral Therapy", (1999) J. Virol. Virol. 73(8):6361-6369.
Berger et al. "Primary and Secondary Metabolism of Pentamidine by Rats", (1992) Antimicrob. Agents Chemother. 36(9):1825-1831.
Bonyhadi et al. "HIV Induces Thymus Depletion In Vivo", (1993) Nature 363:728-732.
Boykin et al. "2-5-Bis[4-(N-alkylamidino)phenyl]furans as Anti-Pneumocystis carinii Agents", (1998) J. Med. Chem. 41: 124-129.
Boykin et al. "Dicationic Diarylfurans as Anti-Pneumocystis carinii Agents", (1995) J. Med. Chem. 38:912-916.
Boykin et al. "Anti-Pneumocystis Activity of Bis-Amidoximes and Bis-O-Alkylamidoximes Prodrugs", (1996) Bioorg. Med. Chem. Lett. 6(24):3017-3020.
Bundgaard "Design and Application of Prodrugs" in Drug Design and Development, (1991) Harwood Academic Publ.: Switzerland pp. 113-191.
Bundgaard et al. "Esters of N,N-Disubstituted 2-Hydroxyacetamides as a Novel Highly Biolabile Prodrug Type for Carboxylic Acid Agents", (1987) J. Med. Chem. 30(3):451-454.
Bundgaard "Design of Prodrugs: Bioreversible Derivatives For Various Functional Groups and Chemical Entities" in Design of Produgs, (1985) Elsevier: Amsterdam, the Netherlands pp. 1-92.
Cardenas et al. "Antifungal Activities of Antineoplastic Agents: Saccharomyces cerevisiae as a Model System to Study Drug Action", (1999) Clin. Microbiol. Rev. 12 (4):583-611.
Das et al. "Synthesis and Antiprotozoal Activity of 2,5-Bis(4-guanylpheny)furans", (1977) J. Med. Chem. 20(4):531-536.
Del Poeta et al. "In Vitro Antifungal Activities of a Series of Dication-Substituted Substituted Carbazoles, Furans, and Benzimidazoles", (1998) Antimicrob. Agents Chemother. 42(10):2503-2510.
Desormeaux et al. "Liposomes as Drug Delivery System: A Strategic Approach for the Treatment of HIV Infection", (1998) J. Drug Targeting 6(1):1-15.
Desormeaux et al. "Antiviral efficacy, intracellular uptake and pharmacokinetics of free and liposome-encapsulated 2',3'-dideoxyinosine", (1994) AIDS 8:1545-1553.
Douek et al. "Changes in thymic function with age and during the treatment of HIV infection", (1998) Nature 396:690-695.
Delgado et al. "The Uses and Propeties of PEG-Linked Proteins", (1992) Critical Reviews in Therapeutic Drug Carrier Systems 9(3,4):249-304.
Danprasert "Synthesis and Characterization of New Amphiphilic Polyesters Based on Poly(Ethylene Glycol)", (1999) Univ. of Massachusetts Lowell pp. 1-107.
Dreborg et al. "Immunotherapy With Monomethoxypolyethylene Glycol Modified Allergens", (1990) Crit. Rev. Ther. Drug Carrier Syst. 6(4):315-365.

El-Samaligy et al. "Ocular Disposition of Nanoencapsulated Acyclovir and Ganciclovir Ganciclovir via Intravitreal Injection in Rabbit's Eye", (1996) Drug Delivery 3:93-97.
Ennis et al. "Structural Factors Influencing the Biodegradation of Imides", (1978) Appl. Environ. Microbiol. 35(1):51-53.
Fishman "Treatment of Infection Due to Pneumocystis carnii", (1998) Antimicrob. Agents and Chemother. 42(6):1309-1314.
Francesconi et al. "2,4-Diphenyl Furan Diamidines as Novel Anti-Pneumocystis carinii carinii Pneumonia Agents", (1999) J. Med. Chem. 42:2260-2265.
Friis et al. "Design And Application of Produgs", (1996) 2.sup.nd Eds. Overseas Publ.: Amsterdam, The Netherlands pp. 351-385.
Gelus et al. "Inhibition of HIV-1 Tat-TAR Interaction By Diphenylfuran Derivatives: Effects of the Terminal Basic Side Chains", (1999) Bioorganic & Medicinal Chemistry 7:1089-1096.
Hall et al. "Anti-Pneumocystis Activities of Aromatic Diamidoxime Prodrugs", (1998) Antimicrob. Agents Chemother. 42(3):666-674.
Halliday et al. "Inhibition of human immunodeficiency virus replication by the sulfonated stilbene dye resobene", (1996) Antiviral Research 33:41-53.
Jamieson et al. "In Vivo Pathogenesis of a Human Immunodeficiency Virus Type 1 Reporter Virus", (1998) J. Virol. 72(8):6520-6526.
Jones "Strategies of Antiviral Drug Discovery", (1998) Antivir. Chem. Chemother. 9:283-302.
Jones et al. "Novel Pentamidine Analogs in the Treatment of Experimental Pneumocystis carinii Pneumonia", (1990) Antimicrobial Agents and Chemotherapy 34 (6):1026-1030.
Katre "The conjugation of proteins with polyethylene glycol and other polymers", (1993) Advanced Drug Delivery Review 10:91-114.
Kitchen et al. "HIV Type 1 Infection in Lymphoid Tissue: Natural History and Model Systems", (1998) AIDS Res. Hum. Retroviruses. Suppl. 3:S-235-239.
La et al. "Ply(ethylene glycol)-Based Micelles for Drug Delivery", (1997) in American Chemical Society Sym. Series 680 Ch. 7 99-116.
Llanos et al. "Does polyethylene oxide possess a low thrombogenicity?", (1993) J. Biomater. Sci. Polymer Ed. 4(4):381-400.
McConnaughie et al. "Design and Synthesis of RNA-Specific Groove-Binding Cations: Implications for Antiviral Drug Design", (1994) J. Med. Chem. 37:1063-1069.
McCune et al. "The SCID-hu Mouse: Murine Model for the Analysis of Human Hematolymphoid Differentiation and Function", (1988) Science 241:1632-1639.
McCune et al. "Suppresion of HIV Infection in AZT-Treated SCID-hu Mice", (1990) Science 247:564-566.
Merrill "Poly(Ethylene Oxide) and Blood Contact", (1992) Poly(Ethylene glycol) Chemistry: Biotechnical and Biomedical Application. Plenum Press NY pp. 199-220.
Miyauch et al. "Studies on Penem and Carbapenem. II. An Improved Synthesis . . . carboxylate", (1990) Chem. Pharm. Bull. 38(4):1077-1078.
Muller et al. "Profound and Sustained Inhibition of Platelet Aggregation by Fradafiban . . . in Men", (1997) Circulation 96:1130-1138.
Namikawa et al. "Infection of the SCID-hu Mouse by HIV-1", (1988) Science 242:1684-1687.
Namikawa et al. "Long-Term Human Hematopoiesis in the SCID-hu Mouse", (1990) J. Exp. Exp. Med. 172:1055-1063.
Okumura et al. "Poly(ethylene oxide)-Bearing Lipids and Interaction of Functionalized Liposomes with Intact Cells" in American Chemical Society Sym. Series Series (1997) 680 Ch. 6 pp. 82-98.
Park et al. "Hydrogels in Bioapplications" in American Cancer Society Sym. Series (1996) 680 Ch 1:1-10.
Paul et al. "Physicochemical Characteristics of Pentamidine-Loaded Polymethacrylate Nanoparticles: Implication . . . Mice", (1998) J. Drug Target 5:481-490.
Pettoello-Mantovani et al. "Saquinavir-Mediated Inhibition of Human Immunodeficiency Immunodeficiency Virus (HIV) . . . Tissues", (1997) Antimicrob. Agents Chemother. 41 41(9):1880-1887.
Pitman "Pro-Drugs of Amides, Imides, and Amines", (1981) Med. Res. Rev. 1(2):189-

214.
Rabin et al. "Use of Standardized SCID-hu Thy/Liv Mouse Model for Preclinical Efficacy Testing of Anti-Human Immunodeficiency Virus Type 1 Compounds", (1996) Antimicrob. Agents Chemother. 40(3):755-762.
Rahmathullah et al. "Prodrugs for Amidines: Synthesis and Anti-Pneumocystis carinii Activity of Carbamates of 2,5-Bis(4-amidinophenyl)furan", (1999) J. Med. Chem. 42:3994-4000.
Sakamoto et al. "Studies on Prodrugs. VI. Preparation and Characterization of . . . Mecillinam", (1987) Chem. Pharm. Bull. 35:642-646.
Sakamoto et al. "Studies on Prodrugs. IV. Preparation . . . Norloxacin", (1985) Chem. Pharm. Bull. 33:4870-4877.
Sehon "Suppression of antibody responses by conjugates of antigens and monomethoxypoly(ethylene glycol)", (1991) Advanced Drug Delivery Reviews 6:203-217.

Sepkowitz et al. "Treatment of Opportunistic Infections in AIDS", (1995) Lancet 346:588-589.
Senior "Fate and Behavior of Liposomes In Vivo: A Review of Controlling Factors", (1987) CRC Critical Reviews in Therapeutic Drug Carrier Systems 3(2):123-193.
Shahrokh et al. "Stability of Alkoxycarbonylamidine Prodrugs", (1998) Pharm. Res. 15 15(3):434-441.
Silverman "Prodrugs and Drug Delivery Systems" in Ed. Academic Press, Inc. San Diego, Cal (1992) pp. 352-401.
Smith "The Process of New Drug Discovery and Development" in CRC Press, inc. Boca Raton, FL (1992) pp. 39-62.
Steck et al. "Trypanosoma rhodesiense: Evaluation of the Antitrypanosomal . . . Dihydrochloride", (1982) Exp. Parasitol. 53:133-144.
Verbiscar et al. "Carbamate Ester Latentiation of Physiologically Active Amines", (1970) J. Med. Chem. 13(6):1176-1179.
Warren et al. "Advances in the Treatment and Prohylaxis of Pneumocystis carinii Pneumonia", (1997) Pharmacotherapy 17(5):900-916.
Weller et al. "Orally Active Fibrinogen Receptor Antagonists 2. Amidoximes as Produgs of Amidines", (1996) J. Med. Chem. 39:3139-3146.
Wilson et al. "Evaluation of Drug-Nucleic Acid Interaction by Thermal Melting Curves", (1997) Methods Mol. Biol 90:219-240.
Wilson et al. "Design and Analysis of RNA Structure-Specific Agents as Potential Antivirals", (1996) J. Mol. Recognit. 9:187-196.
Withers-Ward et al. "Transient renewal of thymopoiesis in HIV-infected human thymic implants following antiviral therapy", (1997) Nat. Med. 3:1102-1109.
Wood et al. "1.5-Bis(4-amidinophenoxy) pentane (pentamidine) . . . sites", (1998) Eur. J. Pharmacol. 353:97-103.
Wood et al. "Pentamidine Is a Potent Inhibitor of [.sup.3 H]Idazoxan Binding to Imidazoline I.sub.2 Receptors", (1999) Ann. NY Acad. Sci. 881:110-113.
Woodle "Poly(ethylene glycol)-Grafted Liposome Therapeutics" in American Chemical Society Sym. Series 680 (1997) Ch. 5 pp. 60-81.
Yeh et al. "Pharmacokinetic Interaction Between Intravenous 2',3'-Dideoxyinosine and and Pentamidine in Rats", (1996) Pharm. Res. 13(4):628-632.
Zalipsky "Chemistry of polyethylene glycol conjugates with biologically active molecules", (1995) Advanced Drug Delivery Reviews 16:157-182.
Zalipsky et al. "Introduction to Chemistry and Biological Applications of Poly (ethylene glycol)", in) American Chemical Society, Sym. Series 680 (1997) Ch. 1 1-13.
Zhao et al. "Novel Degradable Poly(ethylene glycol) Esters for Drug Delivery"in American Chemical Society, Sym. Series 680 (1997) Ch. 28 458-472.
Zhao et al. "Small Changes in Cationic Substituents of Diphenylfuran Derivatives have Major . . . Duplexes", (1995) J. Bioorg. Med. Chem. 3(6):785-794.

ART-UNIT: 1711

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ABSTRACT:

The invention is based in part on the discovery of polymers that can complex with certain types of therapeutic drugs and transport those drugs across cell membranes in cell cultures with demonstrable therapeutic activity. The polymers are designed to overcome some of the known problems of liposomes as drug carriers. The polymers can be used in the development of physiologically stable, non-leaking, non-immunogenic, efficacious and safe targetable drug delivery systems (e.g., for delivery of anti-HIV or anticancer drugs).

44 Claims, 0 Drawing figures

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TITLE: Materials and methods for making improved micelle compositions

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INVENTOR-INFORMATION:

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CLAIMS:

What is claimed is:

1. A method of preparing a biologically active micelle product comprising a biologically active amphipathic compound in association with a micelle; said method comprising the steps of:

a) mixing one or more lipids wherein said combination includes at least one lipid component covalently bonded to a water-soluble polymer;

b) forming sterically stabilized micelles from said combination of lipids;

c) incubating micelles from step (b) with a biologically active amphipathic compound under conditions in which said compound becomes associated with said micelles from step (b) in an active conformation.

2. A method of preparing a biologically active micelle product comprising a biologically active amphipathic compound in association with a micelle; said method comprising the steps of:

a) mixing one or more lipids wherein said combination includes at least one lipid component covalently bonded to a water-soluble polymer with a biologically active amphipathic compound;

b) forming sterically stabilized micelles from the mixture of step (a) under conditions in which said compound becomes associated with said micelles in an active conformation.

3. The method according to claim 1 or 2 wherein said water soluble polymer is polyethylene glycol (PEG).

4. The method according to claim 1 or 2 wherein the amphipathic compound is characterized by having one or more .alpha.- or .pi.-helical domains in its biologically active conformation.

5. The method according to claim 4 wherein the compound is a member of the vasoactive intestinal peptide (VIP)/growth hormone releasing factor (GRF) family of peptides.

6. The method according to claim 5 wherein the peptide is VIP.

7. The method according to claim 1 or 2 wherein the micelles have an average diameter of less than about 20 nm.

8. The method of claim 1 or 2 wherein the combination of lipids consists of distearoyl-phosphatidylethanolamine covalently bonded to PEG (PEG-DSPE).

9. The method of claim 5 wherein the micelles further contain calmodulin.

10. A biologically active micelle product produced by the method of any of one claims 1 through 9.

11. A composition comprising the biologically active micelle product of claim 10 wherein said biologically active amphipathic peptide has an activity selected from the group consisting of anti-oxidant activity, anti-pain, wound healing activity, anti-apoptosis, anti-wrinkling activity, and anti-aging activity.

12. The composition according to claim 11 wherein the composition is a cosmetic.

13. The composition according to claim 11 wherein the composition is a therapeutic.

14. A diagnostic composition comprising the micelle composition according to claim 11 and further comprising a detectable label.

15. The diagnostic composition according to claim 14 wherein the label is selected from the group consisting of a fluorescent label, a radioactive label, a dye, and a compound which enhances magnetic resonance imaging.

16. A diagnostic method comprising the steps of:

preparing a diagnostic composition according to claim 14;

administering a diagnostically effective amount of said composition to a target tissue; and

detecting uptake of the composition at the target tissue by detecting the presence of the label at the target tissue.

17. The method according to claim 16 wherein the label is selected for the group consisting of a fluorescent label, a radioactive label, a dye, and a compound which enhances magnetic imaging resonance.

18. An oral controlled release preparation for the treatment of a gastrointestinal disorder produced according to the method of claim 5 wherein said method further comprises the step of encapsulating the biologically active micelle product.

19. The oral controlled release preparation of claim 18 wherein the gastrointestinal disorder is selected from the group consisting of inflammatory bowel disease, chronic constipation, Hirschprung's disease, achalasia, infantile hypertrophic pyloric stenosis, and ulcers.

20. A method of administering a biologically active amphipathic compound to a target tissue comprising the steps of:

preparing a biologically active micelle product comprising a biologically active amphipathic compound in association with a micelle according to the method of claim 1 or 2; and

administering a therapeutically effective amount of said micelle product to said target tissue.

21. The method according to claim 20 wherein the amphipathic compound in a biologically active conformation is characterized by having one or more .alpha.- or .pi.-helical domains.

22. The method of claim 21 wherein said peptide is a member of the vasoactive intestinal peptide (VIP)/growth hormone releasing factor (GRF) family of peptides.

23. The method of claim 22 wherein said peptide is VIP.

24. A method for preserving a bodily organ, tissue or cell type for transplantation or fertilization comprising the step of incubating said organ in the micelle composition produced according to claim 5.